REMARKS

Replacement Specification

In accordance with 37 C.F.R. §1.125, a replacement specification, both a clean copy and a marked up copy, are provided with this paper. The replacement specification includes section headings, as requested by the Examiner, and a summary section drawn from the detailed description section of the application. The application also includes figure symbols for reference to the figures. An abstract is also provided on a separate sheet. The replacement specification includes no new matter to the application.

Drawings

In accordance with 37 C.F.R. §1.83, drawings, Figures 1 and 2, are provided to show the features of the invention specified in the claims, as requested by the Examiner. The drawings add no new matter to the application.

Claim Rejections Under 35 U.S.C. §112, second paragraph

Claims 1, 14, 16, and 20 are amended to respond to indefiniteness rejections presented under 35 U.S.C. §112, second paragraph. Claim 1 is amended to include the phrase "which comprises inner and outer walls." By specifying the walls of the reservoir means, an appropriate antecedent basis is provided for the term "outer walls". Claims 14 and 16 are amended to provide the proper base claim dependence. Claim 20 is amended in the form of a method claim. Claim 21 is cancelled. The term "means" has been removed from selected claims to correct the antecedent basis for the term "inhaler". As such, the amended claims meet the requirements of 35 U.S.C. §112, second paragraph.

Claim Rejections Under 35 U.S.C. § 102(b)

Claim 1 stands rejected under 35 U.S.C. §102(b) as being anticipated by Bunin (U.S. Patent No. 5,042,472). Claim 1 is patentable over the reference, however, because Bunin does not teach the required elements of the claim.

Amended claim 1 requires a reservoir means "coated on the outer walls, such that the *reservoir means is substantially sealed in the coating* and is *rendered moisture proof*" (emphasis added). Bunin discloses a device for delivering a discrete number of inhaled doses from a plurality of attached compartments, each compartment having a mouth aperture and an air ingress aperture (see abstract and Figures 1 and 3). The apertures are covered by a lidding material, which may be removed to reveal the apertures when the dose is to be inhaled.

Thus Bunin does not teach claim 1 in two respects. First, Bunin does not teach a reservoir means "substantially sealed in the coating." As shown in Figures 1 and 3 of Bunin, the lidding material only covers a portion of the powder medicament [illegible] compartment. Each medicament compartment is not substantially surrounded by the lidding material.

Second, Bunin does not teach a reservoir means with an outer coating such that the reservoir means is "rendered moisture proof" by a coating as required by claim 1. Bunin specifically states that "[t]he multiple powder medicament compartments may be made of any suitable material" (see column 3, lines 42-44). Thus even if the lidding material provides a moisture proof seal, there is no teaching that the *reservoir means* is rendered "moisture proof" by the lidding material since the remaining construction of the compartment may still have a degree of moisture permeability. As noted in the application, plastic walls may be permeable to moisture (see replacement specification, page 1, lines 20-22).

Thus claim 1 is patentable over Bunin since the reference fails to teach the required elements of the claim. Claim 2-4, 11, 12, and 15-19 were also rejected as being anticipated by Bunin. Since these claims all ultimately depend from allowable claim 1, the claims are also patentable over Bunin for the same reasons.

Claim Rejections Under 35 U.S.C. §103(a)

Claims 1-3, 6-14, 19, and 20 stand rejected under 35 U.S.C. §103(a) as being obvious over a combination of Barnes (International Application WO 00/12163) and Mesa (International Application WO 95/15777). The claims, however, are not obvious in light of the references because none of the references, alone or in combination, teaches,

suggests, or motivates one to utilize an inhaler reservoir means with the required elements.

Claim 1 is directed toward an *inhaler* reservoir means "coated on the *outer* walls, such that the reservoir means is substantially sealed in the coating and is rendered moisture proof" (emphasis added). Barnes and Mesa do not teach the required elements of claim 1. Barnes discloses an inhaler in which Parylene (see page 7, lines 16-24) is coated on the inner walls of at least portions of components of an inhaler (see page 8, lines 2-26); no mention is made of coating the outer walls of the inhaler, or a reservoir means, as required by claim 1. Mesa discloses a needle injection device in which parylene may be coated on the outside of the cartridge (a cylindrical dosage container) of the injector (see page 13, lines 6-10). The disclosure makes no reference to (i) an inhaler, or (ii) a reservoir means coated on the outer walls such that the reservoir means is substantially sealed in the coating, both required by claim 1. Thus neither reference alone, or in combination, teaches an inhaler with the required outer wall coated with a moisture proof coating.

Furthermore, no motivation exists to combine Barnes and Mesa to provide the coating required by claim 1. Barnes' motivation for coating portions of the inner walls of an inhaler with parylene is to prevent deposition of the medicament on the internal surfaces and components, which can reduce the efficiency of the inhaler (see page 1, line 32 – page 2, line 6). Thus, Barnes provides no suggestion or motivation for coating the "outer walls" of an inhaler since Barnes only seeks to protect surfaces that come into direct contact with the medicament, and has no motivation to protect the outer wall.

Mesa's motivation is to provide a new design for cartridges of a needle injection system. In particular, Mesa is focused on more reliable and less likely to break cartridges than a typical cartridge constructed of glass (see page 1, line 35 – page 3, line 25). Mesa states that parylene "coating reduces the coefficient of friction of the inner surface of the cartridge and eases movement of the plunger when the plunger is forced forwardly through [the] cartridge" (see page 14, lines 13-17). Thus Mesa does not provide motivation for putting a parylene layer on the *outside wall of an inhaler or the reservoir means of an inhaler* because the reference is concerned with improving the *inner workings of an injection system.*

Whereas the cited references, Barnes and Mesa, are concerned about providing coatings on walls that contact a medicament or other internal surfaces of a needle injector device, the current application provides a coating to the outer walls of an inhaler's reservoir means. The coating has nothing to do with medicament deposition or lowering the friction of the internal workings of the device. Rather, by coating the outer walls, the reservoir means may be "substantially sealed in the coating and . . . rendered moisture proof" (see id., page 3, lines 23-26). The concern of the applicant's invention is moisture that tends to make the powder less "free-flowing" and less effective in providing a correct dose of powder (see replacement specification, page 1, lines 16-19).

Thus claim 1 is not obvious in light of the combination of Barnes and Mesa. Thus, claims 2, 3, 6-14, 19, and 20, all of which ultimately depend from claim 1, are also not obvious.

Claim 5 is rejected as being obvious in light WO 93/16748 in combination with Mesa. However, analogous to the previous remarks, the references do not teach all the elements of the required claim and provide no motivation to make claim 5. WO 93/16748 provides no suggestion or motivation for coating any wall of an inhaler reservoir. Mesa, again, provides no motivation since the reference is drawn to improving the inner workings of an injector, not preventing moisture contamination in an inhaler or inhaler reservoir. As such claim 5 is patentable.

Conclusion

In light of the aforementioned amendments and remarks, claims 1-20 are hereby submitted for acceptance. The Applicants' representative requests the courtesy of a telephone interview, if the Examiner believes such would expedite the prosecution of the application.

Dated: April 22, 2004

Respectfully submitted,

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02245/00109 306422.1

Attorney Docket: 2245/109

Medicament Delivery Device with Moisture Resistant Coating (MARKED UP)

Technical Field

This invention relates to a novel form of reservoir means, such as a medicament capsule and the like and to a delivery device e.g., an inhaler, for use in administering a medicament in such a reservoir means.

Background Art

Many medicament delivery devices, such as inhalers, make use of medicament in a finely divided powder form. The powder may be located within the delivery device, for instance, in a single storage compartment or in a plurality of single dose locations.

One form of inhaler may make use of medicament powder which is located within a frangible, plastic capsule. In use, the capsule is inserted into the inhaler and operation of the inhaler ruptures from the plastic capsule so that the powder may be extracted from the capsule and inhaled by the user.

A problem encountered with many such devices making use of powdered medicament is that, if moisture comes into contact with the powder, it will tend to make it less free-flowing and therefore render the operation of the device less effective because the correct dose of powder cannot be fully delivered.

Moisture may access the powder via several different mechanisms. These include the passage of the moisture through, for example, the plastic wall of encapsulated powder for those inhalers which make use of capsules loaded with medicament powder. For those inhalers which include a storage compartment loaded with powder and from which a dose of powder is accessed by some form of moving part within the inhaler and then presented to an air passageway for inhalation, moisture can access powder within the storage compartment by finding its way along a gap or gaps between the moving parts. In some inhalers there is

the possibility of a "wick" type path being established between the powder in a storage compartment within the inhaler and a location within the inhaler where a dose of medicament is located.

With inhalers where a plurality of single doses of medicament is located within the inhaler, there is again likely to be one or more moving parts, providing gaps along which moisture may travel to access each individual dose of medicament.

It is also possible that moisture can pass through the plastic walls of inhalers and reach the powder contained within the inhaler whether in a single storage compartment or in individual dosage locations.

International Patent Application No WO 00/1216-31 describes the use of a Parylene coating on the inner surface of the metering chamber which is intended to mitigate the deposition of medicament particles on the inner walls of a metered dose inhaler (MDI) for the delivery of medicament via a pressurised aerosol.

Summary of the Invention

A moisture resistant coating, e.g., a Parylene coating, may be used as on a medicament reservoir and/or a medicament delivery device, such as an inhaler (e.g., a dry powder inhaler), to render the device, and especially the medicament chamber, moisture resistant. A reservoir means is provided with a moisture resistant coating in an embodiment of the invention. The reservoir means may be any conventionally known reservoir means, such as a bulk medicament reservoir or one or more single dose reservoir means or a spool and spool carrier. The reservoir means is coated on the outer walls, such that the reservoir means is substantially sealed in the coating and is rendered moisture proof.

In another embodiment of the invention, a medicament delivery device which comprises a medicament reservoir, a medicament delivery passage and a metering member characterised in that the device is provided with a moisture resistant coating on one or more surfaces is provided. Preferably, the whole of the device is substantially provided with a moisture resistant coating.

The moisture resistant coating is preferentially a biocompatible coating. Such coatings include, but are not limited to, sugars.

Brief Description of the Drawings

The foregoing features of the invention will be more readily understood by reference to the following detailed description, taken with reference to the accompanying drawings, in which:

Fig. 1 depicts an embodiment of the invention that is a medicament delivery device (e.g., an inhaler) with a reservoir means, a metering member, and a medicament delivery passage, various surfaces of which are coated with a moisture resistant coating;

Fig. 2A depicts a side view of an embodiment of the invention that is an inhaler holding a plurality of capsules, each capsule including a spool carrier and a spool which may contain a single dose of medicament;

Fig. 2B depicts a view of a plurality of spool carriers for use in an embodiment of the invention; and

Fig. 2C depicts a spool for use with the spool carriers depicted in Fig. 2B, according to an embodiment of the invention.

Detailed Description of Specific Embodiments

We have now surprisingly found that a moisture resistant coating, e.g., a Parylene coating, may be used as on a medicament reservoir and/or a medicament delivery device, such as an inhaler, to render the device, and especially the medicament chamber, moisture resistant.

According to a first aspect of the invention we provide a reservoir means which means is provided with a moisture resistant coating.

In a preferred embodiment, the reservoir means contains medicament such that the reservoir means may be used in conjunction with a delivery device.

The reservoir means may be any conventionally known reservoir means, such as a bulk medicament reservoir or one or more single dose reservoir means. The reservoir means shall not include a pressurised canister for use in inhalation therapy as described in the prior art. When the reservoir means is a single dose reservoir, such as a capsule, e.g., a conventional gelatin capsule, or a spool and spool carrier as described in International Patent

Application No. W093/16748 (as depicted in Figure 1), the coating may be on the inner walls or the outer walls of the reservoir means. However, preferably, the reservoir means **44** is coated on the outer walls **60**, such that the reservoir means **44** is substantially sealed in the coating **60** and is rendered moisture proof. In such a case, the cartridge may also be provided with a moisture resistant coating.

According to a further feature of the present invention, we provide a medicament delivery device which comprises a medicament reservoir as hereinbefore described.

In an especially preferred embodiment the medicament delivery device **80** is also provided with a moisture resistant coating **50**. Such a coating preferentially covers substantially the whole of the delivery device.

When the medicament reservoir means comprises a bulk reservoir, then the medicament delivery device may preferentially include a metering member **41**. The metering member **41** preferably is also provided with a moisture resistant coating.

According to a yet further feature of the invention we therefore provide a medicament delivery device which comprises a medicament reservoir, a medicament delivery passage **45** and a metering member characterised in that the device is provided with a moisture resistant coating on one or more surfaces. Preferably, the whole of the device is substantially provided with a moisture resistant coating.

The moisture resistant coating may be provided on one or more external or internal surfaces of the body of the medicament delivery device. The moisture resistant coating preferentially coats one or more surfaces of the bulk medicament reservoir. Other surfaces of the body of the medicament delivery device may also be provided with a moisture resistant coating.

The moisture resistant coating may be in the form of any material which is effective to prevent moisture accessing the powder **20**. Typically, it may be applied to those surfaces between which there may be a gap due to relative movement between the surfaces when the inhaler is in use. However, the moisture resistant coating may be applied additionally or alternatively to other surfaces including the whole or part of the external surface of the

inhaler in order to prevent moisture passing into the interior of the inhaler through the walls thereof.

The moisture resistant coating should, of course, be sufficiently stable and robust so that damage to the coating during use of the delivery device.

The moisture resistant coating of the invention may be applied to any conventionally known medicament delivery system. However, in a preferred embodiment, the medicament delivery device is an inhaler. Whilst the moisture proof barrier may be applied to any conventionally known inhaler, it is an especially preferred aspect of the invention for the inhaler to be a dry powder inhaler (DPI).

Thus, in a preferred embodiment we provide an inhaler, e.g., a DPI, in which the medicament reservoir is provided with a moisture resistant coating.

Dry powder inhalers are known, such as TECHNOHALER, being developed by Innovata Biomed in the UK. As depicted in Figs. 2A – 2C, WO 93/16748 describes an inhaler **140** which comprises a disc-like cartridge having a plurality of medicament carrying capsules **127** around its periphery. Each capsule **127** comprises a spool carrier **129** which houses a spool **125**. Each spool **125** has a flange **124** at each end which form a tight slidable fit within the body of the spool carrier **129**. The space left between the body of the spool **125** and the spool carrier **129** is filled with an appropriate medicament.

In a preferred embodiment, an example of which is depicted by Figs. 2A – 2C, we provide a dry powder inhaler **140** wherein the medicament reservoir comprises one or more individual medicament capsules **127**, e.g. spool carriers **129** and wherein each medicament capsule **127** is provided with a moisture resistant coating. Preferably, the medicament capsule is sealed in a moisture resistant coating.

A variety of medicaments may be administered by using the inhaler of the invention. Such medicaments are generally (but not limiting), bronchodilators I or other anti asthma drugs or antibiotics. Such medicaments include, but are not limited to β_2-agonists, e.g., fenoterol, formoterol, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol and terbutaline; non-selective beta-stimulants such as isoprenaline; xanthine bronchodilators, e.g.,

theophylline, aminophylline and choline theophyllinate; anticholinergics, e.g., ipratropium bromide; mast cell stabilisers, e.g., sodium cromoglyeate and ketotifen; bronchial anti-inflammatory agents, e.g., nedocromil sodium; and steroids, e.g., beclomethasone dipropionate, fluticasone, budesonide and flunisolide; and combinations thereof.

Specific combinations of medicaments which may be mentioned include combinations of steroids, such as, beclomethasone dipropionate, fluticasone, budesonide and flunisolide; and combinations of to β_2-agonists, such as, formoterol and salmeterol. It is also within the scope of this invention to include combinations of one or more of the aforementioned steroids with one or more of the aforementioned β_2-agonists.

Further medicaments may include proteinaceous compounds and/or macromolecules, for example, leuprolide and alpha interferon; hormones, such as insulin, human growth hormone, parathyroid hormone; growth factors, anticoagulants, immunomodulators, cytokines and nucleic acids.

According to a yet further feature of the invention we provide a method of treating a respiratory disorder which comprises the administering of a therapeutically effective amount of a pharmaceutically active agent to a patient suffering from such a disorder.

The moisture resistant coating is preferentially a biocompatible coating. Such coatings include, but are not limited to, sugars.

Polymers of poly-para-xylylenes are known as parylene. This material is a conformal polymer film which has been used in a number of applications, including electronics circuits and sensor, where environmental and dielectric isolation is required.

We further the use of a parylene in the manufacture of a moisture resistant capsule as hereiribefore described.

Parylenes are thermoplastic polymers that are capable of polymerising on surfaces from an active monomer gas, without the presence of a liquid. The process is capable of producing very thin layers of polymer and, indeed, a layer of from 10 to 20 microns may be sufficient to protect inhalers and their parts from ingress of moisture.

The polymerisation process takes place at room temperature without solvents and additives. Since the parylene is applied as a gas it conforms to the topography of the surface which it contacts. Since the process does not involve a liquid phase, there is no pooling and bridging during application. The coating is free of pinholes even if the coating has a thickness of less than one micron. As well as being resistant against moisture, parylene is also resistant against other media including hydrocarbons, acids and blood.

The coating may be applied in a single vacuum-coating operation in a thickness from 0.025 to 75 microns and can be controlled accurately to ± 10% of the final thickness.

Attorney Docket: 2245/109

Medicament Delivery Device with Moisture Resistant Coating

Abstract

There is described a reservoir means which means is provided with a moisture resistant coating, the reservoir means is especially adapted to contain a medicament. There is also described a medicament delivery device which comprises a medicament reservoir, a medicament delivery passage and a metering member characterised in that the device includes a surface or surfaces provided with a moisture resistant coating. The device is especially an inhaler, e.g., a dry powder inhaler. A method of treating a respiratory disorder is also described which comprises administering of a therapeutically effective amount of a pharmaceutically active agent to a patient suffering from such a disorder.